

Medical Information

Drug Choice for Treatment of Hypertension at 'Step 2'

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THE JOINT NATIONAL COMMITTEE on Detection, Evaluation, and Treatment of High Blood Pressure has recommended a "stepped care approach,"¹ initiating treatment with a small dose of an antihypertensive drug, increasing the dose of that drug and, as needed, adding other drugs. At *step 1* they recommend that a thiazide-type diuretic be prescribed. However, approximately 60 percent to 70 percent of hypertensive patients require a second drug at *step 2*.² The Committee suggests reserpine, methyldopa or propranolol hydrochloride, or a combination of these, as the second drug of choice.

The choice of drug at *step 2* is important for individual patients, and in a public health context as well. About 20 percent of adults in the United States have hypertension; consequently, in sheer numbers this is one of the most important drug choices that the physician makes.

Choice of a Step 2 Drug

Reserpine, methyldopa and propranolol appear to be equally effective. The most recent Veterans Administration Cooperative Study³ concludes that "the reserpine-thiazide combination when subjected to controlled clinical trials has uniformly demonstrated antihypertensive effectiveness equal or superior to that of other antihypertensive agents." Unfortunately, this study did not concurrently compare the efficacy of reserpine with methyldopa-thiazide combinations. Smith and co-workers reported on a clinical trial in 1966 com-

TABLE 1.—Side Effects of Step 2 Antihypertensives

Side Effects	Methyl- dopa	Propran- olol	Reser- pine
Depression	±	±	±
Abnormal liver function test	+	0	0
Chronic active hepatitis	+	0	0
Positive Coombs test	+	0	0
	(20 percent)		
Hemolytic anemia	±	0	0
Hypersensitivity, myocarditis, colitis	?	0	0
Nasal congestion	0	0	+
Bad dreams	+	+	+
Increased gastric acid	0	0	+
Bradyarrhythmia	0	+	±
Increased asthma	0	+	0
Heart failure	0	±	0
Impotence	+	±	?
Abnormal ejaculation	0	+	0

± = infrequent
+ = relatively common
0 = not reported

paring these drugs in 189 patients and concluded that "neither alpha-methyldopa alone, in an average dose of 1.5 grams, or in combination with chlorothiazide, the latter at 1 gram daily, was as effective" as rauwolfia and chlorothiazide.⁴ Other studies have shown no significant difference between the antihypertensive effects of reserpine and methyldopa.⁵

With no evidence of significantly greater antihypertensive effect of methyldopa, propranolol or reserpine, on what basis is a drug selected for a patient needing *step 2* medication? Criteria of importance to physician and patient include (1) frequency and seriousness of *side effects*, (2) cost, (3) number of tablets per day, (4) frequency of dosage and (5) significance of an omitted dose.

Side Effects

The major reason for the frequent avoidance of reserpine has been the possibility of provoking serious depressive reactions, including suicide. Textbooks and journals are literally crammed with warnings about this serious side effect with frequent statements that reserpine should not be used or used only with caution.

However, a careful review of the literature finds no evidence of a significantly high frequency of depression when reserpine is taken in therapeutic dosages (Table 1). In fact, reports of depression are based uniformly on clinical trials in which larger than therapeutic doses and, indeed, toxic doses of reserpine were administered. The article by Quetsch and associates,⁶ itself a review of other studies on depressive reactions caused by reser-

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Submitted September 7, 1978.

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pine, shows that the doses ranged from a minimum of 0.4 mg up to 1.0 mg daily. Muller in 1955 described "severe mental illness" in 7.5 percent of patients receiving rauwolfia therapy.⁷ The lowest dose in this series was 0.75 mg per day. Of the five patients who had such effects, three were receiving 2 mg or more per day, eight to ten times more than the therapeutic dose. Schroeder and Perry⁸ described psychotic behavior with agitated depression states and suggested that doses were not abnormally high; in fact, all of the patients were taking at least 1 mg of reserpine daily.

Further review of the literature has *not* shown an incidence of depression from reserpine administration any greater than other antihypertensive drugs when therapeutic doses (that is, up to 0.25 mg a day) are used. For example, Gibb and associates⁵ conducted a double-blind study of 60 matched hypertensive patients treated with bethanidine, alpha-methyldopa and reserpine; they showed that reserpine produced the *smallest incidence of side effects*. Further emphasizing the relative safety of reserpine were the Veterans Administration Cooperative Study Group reports on antihypertensive agents in 1962, 1967 and 1970, in which reserpine proved to be a consistently effective agent when combined with thiazide and was *no more toxic than other antihypertensive drugs*. The 1977 Veterans Administration study¹ compared various combinations of antihypertensive drugs and found that the combination of propranolol, thiazide and hydralazine, and the combination of reserpine and thiazide were most effective. The frequency of depression and lethargy were essentially *equal* in the propranolol-plus and the reserpine-plus groups. Reserpine provoked excessive side effects in comparison with the other drug combination *only* in the category of nasal stuffiness and, possibly, dyspnea, but *not in depression*.

Lassitude and somnolence are described in almost all reports on the side effects of alpha-methyldopa. (One wonders how carefully the differentiation is made between these symptoms and depression: When the patient reports "I have no energy and I feel low," which side effect is tabulated?) Positive Coombs tests are found in 20 percent of patients on a regimen of alpha-methyldopa but only in about 10 percent of this group do hemolytic anemia or thrombocytopenic purpura develop. However, as Böttiger and Westerholm⁹ have pointed out, methyldopa is the

TABLE 2.—*Dosage and Cost of Step 2 Antihypertensives*

Factor	Methyldopa	Propranolol	Reserpine
Efficacy	Equal	Equal	Equal
Daily doses	3-4	2-4	1
Number of tablets daily	2-6	4-12	1
Effect of omitted dose	Significant	Significant	Minimal
Monthly cost	\$12.00	\$8.50	\$3.30

leading cause of drug-induced hemolytic anemias (some 47 percent in their series), and, rarely, deaths have occurred. Methyldopa-induced hepatitis has been reported frequently.^{10,11} Although the etiologic relationship is not certain, there have been recent reports of what appear to be methyldopa-induced myocarditis¹² and colitis. Impotence is another serious side effect not uncommonly described with alpha-methyldopa.

Propranolol is generally considered to be relatively free from disturbing side effects, but in the Veterans Administration Cooperative Study there was essentially no difference in frequency of lethargy, impotence, depression, headache, vertigo, ulcer symptoms and nightmares between reserpine-treated and propranolol-treated groups. Propranolol is frequently mentioned as a cause of congestive heart failure, but that appears to be rarer than had been expected. Bradyarrhythmias, bronchospasm in a patient with asthma and decreased adrenergic response to hypoglycemia in a diabetic patient receiving insulin are side effects that must be taken into consideration in deciding whether to use propranolol. In fact, bronchospasm occurs in 2 percent to 10 percent of patients, excluding those with asthma or previous bronchospasm.

Cost and Dosage

There are immense discrepancies among the costs of these medications (Table 2). Methyldopa will cost a patient at least 30 times as much as reserpine, and propranolol 25 times as much as reserpine, based on actual 1977 cost in a San Francisco outpatient department for a one month's supply at average dosages. This cost difference alone, in light of equal efficacy, is reason enough to seriously consider reserpine as the first drug to try at the *step 2* level. Obviously, the decision must be based on individual trials and consideration of the side effects of each drug.

Frequency of dosage and the number of tablets per day is less important than either side effects or cost; however, it is not unreasonable to assume that a patient is more likely to comply with a

therapeutic regimen if medication is required only once a day rather than three or four times per day. Reserpine should be prescribed only on a once per day basis. Propranolol is usually prescribed as four daily doses, although there is evidence suggesting that three, or perhaps even two, doses daily will maintain an antihypertensive effect.¹³ Methyldopa is usually given three to four times a day; here also there is evidence that two doses a day are satisfactory and, in fact, one report indicates that once daily dosage is adequate.

Most patients using methyldopa take four to six tablets a day. A review of outpatient charts on patients taking methyldopa showed that some patients were given prescriptions for 8 to 12 tablets (250 mg tablets) per day. Propranolol is usually prescribed as 4 to 12 tablets daily. With reserpine, only one tablet per day should be taken.

It is probably an unusual patient who remembers to take every dose of prescribed medication. This is especially likely to be true in an asymptomatic condition such as hypertension. Because of long half-life (the slow disappearance of the antihypertensive effect) of reserpine, a missed dose has essentially no effect. The more rapid disappearance of antihypertensive effect of both propranolol¹⁴ and methyldopa force a patient much more often to consider "Did I or did I not take my pill?"

Comment

Let us return to the hypothetical patient with essential hypertension that has not responded well to therapy with a thiazide diuretic. We now plan to take *step 2* in our treatment plan. From the above discussion, is there any reason to choose one drug over another? There is at present no overwhelming evidence that one is more or less efficacious than the other. Each of the three drugs has toxic side effects, but reserpine is "no more toxic than other antihypertensive drugs,"³ and it seems clear that depression as a serious effect of reserpine has been overemphasized. As to frequency of dosage and number of tablets required per day, reserpine is clearly the preferable drug. It is likewise preferable in terms of its much longer half-life so that poor compliance has considerably less likelihood of having significant effect on the desired antihypertensive action. Finally, reserpine costs *between 25 times and 35 times less* than methyldopa and propranolol. Therefore, reserpine appears to be a reasonable

first choice for most patients at *step 2* in the treatment of hypertension.

Summary

The Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure has recommended a "stepped-care approach," initiating treatment with a small dose of a thiazide-type diuretic, and, as needed, adding other drugs. In approximately 70 percent of hypertensive patients a second drug at *step 2* is required. The choice of the antihypertensive drug to be used at *step 2* is an important one. The recommended drugs—reserpine, alpha-methyldopa and propranolol—are compared on several bases. Reserpine appears to be a reasonable first choice for most patients at *step 2* in the treatment of hypertension.

Addendum

Since acceptance of this paper, F. A. Finnerty, Jr., MD; A. Gyftopoulos, MD; C. Berry, LPN, and A. McKenney, LPN have reported (JAMA 241: 579-581, Feb 9, 1979) a clinical trial comparing the *step 2* combination drugs of a thiazide plus either reserpine, methyldopa or propranolol. They also conclude that the reserpine-thiazide combination offers distinct advantages—on the same grounds as those outlined in this paper.

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